REMARKS

This is a response to the Office Action, dated January 14, 2009 ("Office Action"). Allowance and reconsideration of the application in view of Applicants' foregoing amendments and ensuing remarks are respectfully requested. Claims 4-5 have been amended and claims 14-17 and 24-28 have been canceled. Claims 1-13 and 18-23 remain pending.

Claims 4-5 have been amended to replace the term *molecular mass* with the term *weight-averaged molecular weight (Mw)*. Support for this amendment may be found throughout the specification and claims as originally filed.

Election/Restriction

Examiner maintains that the previous restriction requirement is proper and final, and acknowledges Applicant's election with traverse of Group I, claims 1-23, drawn to a drug delivery molecule, as well as election of a targeting molecule that promotes penetration of the blood-brain barrier as a targeting module and of the prodrug antisense molecule targeting alpha-4-laminin, in the reply filed on October 20, 2008. Although in no way conceding that the requirement is proper, Applicants have canceled claims 14-17 and 24-28 in response.

Priority

Examiner finds that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120 in that the provisional application 60/527,300 does not provide support for a targeting molecule that promotes penetration of the blood brain barrier. Therefore, Examiner asserts, the instant claims are accorded the international filing date of the present application which is December 2nd, 2004. In response, Applicants respectfully submit that an embodiment that includes a targeting molecule for penetrating the blood brain barrier would have been readily recognized by one of skill in the art based upon the provisional application's disclosure. The provisional application describes

molecular modules attached to a polymalic acid backbone, including a targeting antibody module against transferrin receptor for receptor-mediated endocytosis. As recognized by one of skill in the art, the transferrin receptor is known to be expressed on endothelium cell surfaces that function as the blood brain barrier. A targeting module directed against transferrin receptor mediated endocytosis supports claims directed toward targeting molecules that promote penetration of the blood brain barrier, based upon the known expression of transferrin receptors by endothelial cells of the blood brain barrier. Thus, Applicants respectfully submit that the present application is entitled to the priority date of December 5th, 2003.

35 U.S.C. §112, 2nd ¶ - Claims 4-5

Examiner rejected claims 4 and 5 under 35 U.S.C. §112, 2nd ¶ as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Examiner asserts that claims 4 and 5, which require molecular weight as a molecular mass, is indefinite because there are at least three different ways to describe molecular weight of a polymer, namely the average molecular weight (Mn), weight average molecular weight (Mw), and the volume average molecular weight (Mv). In response, Applicants submit that the molecular mass ranges referred to in the relevant claims describe molecular weight as weight average molecular weight (Mw), as supported by the specification and claims as originally filed. Applicants have amended claims 4 and 5 so that the term molecular mass is replaced with the term weight-averaged molecular weight (Mw), and therefore respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. §103(a) – Claims 1-13 and 20

Examiner rejected claims 1-13 and 20 under 35 U.S.C. §103(a) as being unpatentable over LaFleur, *et al.*, and Cammas, *et al.* Examiner asserts that LaFleur, *et al.* teaches a biodegradable polymeric drug delivery system comprising polymalic acid, PEG and reporter moieties, with agents including KDI antisense oligonucleotides as well as agents that promote the penetration of the blood-brain barrier. Cammas, *et al.*, Examiner asserts, teaches polymalic acid as a drug carrier that has lateral carboxylic acid functions which allow the introduction of a

biologically active molecule and targeting moiety by chemical modifications. Thus, Examiner asserts, it would have been obvious to one of skill in the art to use the polymalic acid polymer taught by Cammas, *et al.* to conjugate the targeting, prodrug, pore-forming, PEG and reporter moieties taught by LaFleur, *et al.* In response, Applicants respectfully submit that claims 1-13 and 20 are patentable over the comination of LaFleur, *et al.* and Cammas, *et al.*

First, in response, Applicants submit that Examiner has misinterpreted the LaFleur, *et al.* reference. While LaFleur, *et al.* may describe each of the aforementioned agents, it is in the context of their singular use rather than as moieties that may act while conjugated together. Although LaFluer, *et al.* may describe both a drug delivery system and the aforementioned agents, they are not part of the same embodiment and are thus not applicable to the present invention.

Second, many of the cited agents are described by LaFleur, *et al.* in the context of performing assays and not as potential components of a drug delivery system. For example, citing column 143, line 58 to column 146, line 62 of the reference, Examiner asserts that the use of antisense oligonucleotides is described as a potential agent for delivery with the polymeric drug delivery system. However, these antisense techniques are in fact described by the reference as possible antagonists for screening additional compounds related to a KDI compound, and not in conjunction with drug delivery systems of the KDI compound itself.

Third, the scaffold described by LaFleur, *et al.* is not covalently linked to the active modules, and thus cannot be compared to the present invention. For example, Examiner cites column 151, line 49 to column 152, line 3 of LaFleur, *et al.* for the assertion that the reference teaches a biodegradable polymeric drug delivery system wherein the polymer comprises polymalic acid and PEG. However, LaFleur, *et al.* does not teach that PEG is covalently attached to polymalic acid, or for that matter, if PEG is an active moiety that is even associated with the polymalic acid. The present application is limited to modules, such as PEG, that are *covalently* linked to the molecular scaffold. As understood by one of skill in the art, a complex such as that described by the reference is held together by *noncovalent* forces. By definition, the conjugate described by the present application is not a complex. The conjugate of the present application is very different chemically than the hypothetical complexes described by LaFleur, *et al.* because of the covalent attachment of groups. Unlike the noncovalent complexes described by LaFleur, *et al.* which tend to decompose during delivery, the covalent attachments described

by the present application allow greater stability in plasma and are thus more useful for targeted drug delivery to specific tissue in vivo and in treatment. Similarly, Examiner cites column 152, lines 17-20, for the assertion that LaFleur, *et al.* teaches that molecular weight and hydrophobicity of the drug delivery system may be modified to obtain the desired drug release. However, the reference is referring to noncovalent embedding of antisense oligonucleotides in polymers.

Fourth, Applicants submit that claims 3-5 are further distinguished from the reference as they are specifically limited to a molecular scaffold that is poly (ß-L-malic acid). Unlike other forms of polymalic acids, this polymer is completely biodegradable in mammals to water and carbon dioxide because it contains only L-malic acid, whereas D-malic acid as contained in other forms of polymalic acid such as poly(D-malic acid) or in poly(D,L-malic acid) is not degradable.

Finally, while the present application is limited to modules that either promote cellular uptake by a target cell or alter cellular metabolism, the cited reference describes neither. For example, Examiner cites column 72, lines 7-29 for the assertion that LaFleur, *et al.* teaches that antibodies for cell-targeting may be conjugated to the drug compositions. However, the reference does not describe the antibody as a targeting module for promoting cellular uptake. The reference instead describes the use of antibodies against KDI where the antibody is utilized as an analytical agent. This is a completely different application for the module than what is described by the present application, which is that antibodies are used to target antigens on cell surfaces to direct the multicomponent multifunctional drug carrier to the receipient cell by crossing both the blood vessel endothelial cell barriers and the recipient cell membrane by first binding to the surface antigen and then internalization.

Applicants also respectfully submit that Examiner has misinterpreted Cammas, *et al.* Examiner asserts that Cammas, *et al.* teaches polymalic acid as a drug carrier that has lateral carboxylic acid functions which allow the introduction of a biologically active molecule and targeting moiety by appropriate chemical modifications, citing p.273, second column of the reference. However, in response, Applicants submit that the reference is in fact discussing the use of polymalic acid in the production of macromolecular micelles and nanoparticles, but not of soluble nanoconjugates. Unlike the present application, Cammas, *et al.* discusses the loading of the drug to the various entities by physical forces and not by covalent attachment. Additionally, Examiner asserts that Cammas, *et al.* teaches polymalic acid polymers having alkyl pendant

groups, lateral functional groups, and biologically active molecules as pendant groups and that the lateral chemical functions can be modified to requirements (p. 273-274 of the reference) and that polymalic acid polymers can be obtained that have one or several pendant groups and high molecular weight (p. 273, first paragraph of the reference). However, again, Applicants submit that Cammas, *et al.* is discussing a very different type of chemistry than what is described by the present application. The reference describes the synthesis of various forms of polymalic acid conjugated to very few conjugates by anionic ring-opening polymerization of malolactonic acid esters, appropriately derivatized at the alpha-carboxylic group in the monomer before polymerization. This is in total contrast to the present invention, where synthesis allows covalent attachment of nucleic acids and proteins. Attachment of proteins and nucleic acids via the ring opening polymerization of corresponding malolactonic derivatives described by Cammas, *et al.* would not be chemically feasible. The product would be inactive in targeted drug delivery due to the degradability and reactivity of proteins and nucleic acid in uncontrolled side reactions during the polymerization reaction.

For the reasons discussed above, Applicants respectfully submit that claims 1-13 and 20 under 35 U.S.C. 103(a) are patentable over the combination of LaFleur, *et al.* and Cammas, *et al.* and would not have been obvious to one of skill in the art.

35 U.S.C. §103(a) – Claims 18-19

Examiner rejected claims 18 and 19 under 35 U.S.C. § 103(a) as being unpatentable over LaFleur, *et al.* and Cammas, *et al.*, and further in view of Saito, *et al.* Examiner asserts that one of skill in the art would find it obvious that the disulfide bonds taught by Saito, *et al.* would be appropriate for linking antisense oligonucleotides to the polymalic acid polymer. In response, for the reasons discussed above, Applicants respectfully submit that the present invention would have been nonobvious at the time of filing to one of skill in the art in light of the combination of LaFleur, *et al.*, Cammas, *et al.* and further in view of Saito, *et al.*

35 U.S.C. §103(a) – Claim 21

Examiner rejected claim 21 under 35 U.S.C. § 103(a) as being unpatentable over LaFleur, *et al.* and Cammas, *et al.*, and further in view of Summerton, *et al.* Examiner asserts that it would have been obvious to one of skill in the art to incorporate morpholino antisense oligonucleotides for the modified antisense oligonucleotides taught by LaFleur, *et al.*, because Summerton, *et al.* teaches the benefits of using such morpholino antisense oligonucleotides. In response, Applicants respectfully submit that the present invention would not have been obvious to one of skill in the art in light of the combination of LaFleur, *et al.* and Cammas, *et al.*, and further in view of Summerton, *et al.* for the reasons discussed above.

35 U.S.C. §103(a) – Claims 22-23

Examiner rejected claims 22 and 23 under 35 U.S.C. § 103(a) as being unpatentable over LaFleur, *et al.* and Cammas, *et al.*, and further in view of Khazenzon, *et al.* Examiner asserts that Khazenzon, *et al.* teaches morpholino antisense oligonucleotides targeting α4-laminin, and it would have been obvious to one of skill in the art to formulate the antisense oligonucleotides described by Khazenzon, *et al.* in the polymalic acid drug delivery molecule taught by LaFleur, *et al.* and Cammas, *et al.* In response, Applicants respectfully submit that the present invention would not have been obvious to one of skill in the art in light of the combination of LaFleur, *et al.* and Cammas, *et al.*, and further in view of Khazenzon, *et al.* for the reasons discussed above.

All of the claims in the application are believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
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